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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,606	02/27/2004	Mary E. Brunkow	601117-109	9642

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,606	BRUNKOW ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88,89 and 91-100* is/are pending in the application.

4a) Of the above claim(s) *97-100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88,89 and 91-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's amendment of the claims filed on 21 August 2007 is acknowledged.

Claims 1-87 and 90 have been cancelled. Claims 88, 89, 91-100 are pending. Claims 97-100 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 88, 89 and 91-96 are under examination.

Claim Rejections Withdrawn

The rejection of claims 88-96 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's amendment of the claims and the argument that Applicant has provided a representative number of species for the genus.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The amended claims 88, 89 and 91-96 remain rejected under 35 U.S.C. § 112, first paragraph, as being lack of enablement for reasons set forth in the previous office action.

Applicant argues that the breath of the genus of the claimed invention is not limited, and it is characterized structurally by the hybridization conditions and by the structural feature of retaining a cysteine backbone, and functionally by retaining the ability to alter bone density. Applicant argues that modification of polynucleotides and expression of variant polypeptides, and preparation of antibodies to polypeptides was routine in the art. Applicant argues that the specification has a great deal of guidance regarding the modification of polynucleotide, for example, the cysteine backbone of the protein should be generally conserved. The specification provides seven different sequences of native mammalian and variant human cDNA (SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15), from which one can determine which amino acids and regions are conserved among mammalian species, by sequence alignment. Applicant further argues that the recited hybridization conditions detect molecules about 80% homologous to SEQ ID NO: 1, which is relatively high in homology. Applicant also argues that the scope of the polynucleotides recited in claim 89 (i.e., 90% homology) parallels issued claims in U. S. Patent No: 6,395,511. Applicant argues that having adequately described and enabled a novel protein that is 90% identical to a reference sequence, it would be routine experimentation to make antibodies to such proteins.

Applicant's argument has been fully considered, but has been found to be partially persuasive.

The claims have been amended to encompass: 1) an isolated antibody or antigen-binding fragment thereof which specifically binds to a polypeptide, wherein the polypeptide is encoded by a first polynucleotide capable of binding under conditions of high stringency to a second polynucleotide selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15, and fully complementary sequences thereto, and wherein the polypeptide retains a cysteine backbone comprising eight cysteines and retains the ability to alter bone density; and 2) an isolated antibody or antigen binding fragment thereof which specifically binds to a polypeptide encoded by a polynucleotide having at least 90% identity to a full length sequence selected from SEQ ID NOs: 1, 5, 9, 11, 13 and 15, or a complementary sequence thereof, and wherein the polypeptide retains a cystein backbone comprising eight cysteines and retaind the ability to alter bone density.

Applicant's amendment of the claims is not sufficient to overcome the 112 first paragraph rejection as failing to comply with the enablement requirement, because the claims still read on antibodies that bind to polypeptides encoded by the non-coding strand of the polynucleotides of SEQ ID NOs: 1, 5, 9, 11, 13 and 15, or a fragment thereof. As set forth previously, the claim recitations of "the polypeptide is encoded by a first polynucleotide capable of binding under conditions of high stringency to a second polynucleotide selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15, and fully complementary sequences thereto" and "a polypeptide encoded by a polynucleotide having at least 90% identity to a full length sequence selected from SEQ ID NOs: 1, 5, 9, 11, 13 and 15, or a complementary sequence thereof" encompass

antibodies or antigen-binding fragments thereof which bind to polypeptides encoded by the non-coding strand of the polynucleotides of SEQ ID NOs: 1, 5, 9, 11, 13 and 15, and the resulting amino acid sequences would be completely different from the polypeptides encoded by SEQ ID NOs: 1, 5, 9, 11, 13 and 15. The specification has not provided any example for antibodies that bind to such polypeptides. Moreover, "a complementary sequence thereof" reads on a fragment of nucleotide sequence (can be as few as three nucleotides) that is complementary to the polynucleotides of SEQ ID NOs: 1, 5, 9, 11, 13 and 15.

Further, the claims have been amended to add the structural and functional limitations of "wherein the polypeptide retains a cysteine backbone comprising eight cysteines and retains the ability to alter bone density". However, the term "alter bone density" can be interpreted as "increase" and "decrease" bone density. The specification discloses that the TGF-β binding proteins, or BEER polypeptides, of the instant invention bind to BMP-5 and BMP-6 (see Figure 5). The specification discloses that molecules which are suitable for use in increasing bone mineral content are those molecules which decrease the binding of TGF-β binding protein to a member or members of the TGF-β superfamily (page 41, lines 14-17), and that mutants of TGF-β binding protein which compete with the native TGF-β binding proteins' ability to block the activity of a particular TGF-β family member should lead to an increased bone density (page 48, lines 13-20). The specification, however, does not provide sufficient guidance for making such antagonistic variants. The seven members of the Beer polypeptides encoded by SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15, are all BMP

antagonists. Further, the recited structural features are also present in other TGF-β binding proteins, such as Dan, Cerberus, Gremlin and SCGF. These proteins possess a nearly identical cysteine disulfide scaffold (see Figure 1), however, the homology in other regions of the polypeptides is very low. These proteins also act as BMP antagonizing proteins. The specification does not provide sufficient teachings as to what changes can be made to the molecules to function as TGF-β binding protein antagonists (to increas the BMP activities). While Applicant describes a screening assay for inhibition of TGF-β binding protein binding to TGF-β family members, however, the enablement requirement of 35 U.S.C. 112, first paragraph stipulates one of ordinary skill in the art to make and use the invention, rather than "make and test". Without guidance for the detailed structural features of the molecules, it would requires tremendous undue experimentation to generate the infinite number of variants recited in the claims, and determine their effects on bone density. Therefore, the enablement requirement is not fulfilled.

Double Patenting

The rejection of amended claims 88, 89, 91-100 under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of U. S. Patent No: 6,803,453, is maintained. Applicant has not filed a terminal disclaimer.

New Grounds of Objections/Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 88 and 89 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 88 is indefinite because it encompasses a nucleic acid molecule which hybridizes under "**high stringency**" conditions. Though the specification on page 4, lines 15-19, and on page 28, lines 14-20, describes various hybridization and wash conditions, they are exemplary. The term **high stringency** is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

Claims 88 and 89 are indefinite for the recitation of "alter bone density". Since the specification provides no definition for the term "alter bone density", the metes and bounds of the claimed invention cannot be determined.

Claim Objections

Claim 89 is objected to because of the following informalities:

There is a typographical error in the claim "which specifically binds to a a polypeptide". Appropriate correction is required.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
September 25, 2007

Eileen B. O'Hara
EILEEN B. O'HARA
PRIMARY EXAMINER